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Review article

Host genetics of response to porcine reproductive and respiratory syndrome in nursery pigs

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ABSTRACT

PRRS is the most costly disease in the US pig industry. While vaccination, biosecurity and eradication effort have had some success, the variability and infectiousness of PRRS virus strains have hampered the effectiveness of these measures. We propose the use of genetic selection of pigs as an additional and complementary effort. Several studies have shown that host response to PRRS infection has a sizeable genetic component and recent advances in genomics provide opportunities to capitalize on these genetic differences and improve our understanding of host response to PRRS. While work is also ongoing to understand the genetic basis of host response to reproductive PRRS, the focus of this review is on research conducted on host response to PRRS in the nursery and grow-finish phase as part of the PRRS Host Genetics Consortium. Using experimental infection of large numbers of commercial nursery pigs, combined with deep phenotyping and genomics, this research has identified a major gene that is associated with host response to PRRS. Further functional genomics work identified the GBP5 gene as harboring the putative causative mutation. GBP5 is associated with innate immune response. Subsequent work has validated the effect of this genomic region on host response to a second PRRSV strain and to PRRS vaccination and co-infection of nursery pigs with PRRSV and PCV2b. A genetic marker near GBP5 is available to the industry for use in selection. Genetic differences in host response beyond GBP5 appear to be highly polygenic, i.e. controlled by many genes across the genome, each with a small effect. Such effects can by capitalized on in a selection program using genomic prediction on large numbers of genetic markers across the genome. Additional work has also identified the genetic basis of antibody response to PRRS, which could lead to the use of vaccine response as an indicator trait to select for host response to PRRS. Other genomic analyses, including gene expression analyses, have identified genes and modules of genes that are associated with differences in host response to PRRS and can be used to further understand and utilize differences in host response. Together, these results demonstrate that genetic selection can be an additional and complementary tool to combat PRRS in the swine industry.

1. Introduction

Porcine reproductive and respiratory syndrome (PRRS) is the most costly viral disease in the U.S. and around the world (Holtkamp et al., 2013). PRRS affects both the reproductive and grow-finish sectors of the pork industry through a decrease in reproductive health, an increase in mortality and morbidity, and reductions in the rate and efficiency of growth (Zimmerman et al., 2012). PRRS virus (PRRSV) also functions as a cofactor in other disease syndromes, such as porcine respiratory disease complex (PRDC) and PCV-associated disease (PCVAD) (Gillespie et al., 2009; Hansen et al., 2010). Holtkamp et al. (2013) estimated the annual cost in production-related losses of PRRS in the US at $664 million ($1.8 million/day), which was 18% greater than costs estimated in 2005 (Neumann et al., 2005), despite large efforts to control the disease through improvements in veterinary health management, biosecurity, disease elimination, and vaccination (Darwich et al., 2010; Huang and Meng, 2010; Chand et al., 2012). Additional costs attributed to PRRS for veterinary, biosecurity and other outbreak-related costs were estimated at $478 million (Holtkamp et al., 2013), putting the cumulative cost over $1 billion per year. Fifty-five percent of the costs were attributed to the growing pig sector (Holtkamp et al., 2013). Vaccination for protection against PRRSV

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infection has generally been unsuccessful, primarily due to the high degree of antigenic and genetic drift in viral structural and non-structural proteins and the capacity of the PRRS virus to subvert early innate immune responses (Fang et al., 2007; Kimman et al., 2009; Mateu and Diaz, 2008; Murtaugh and Genzow, 2011; Neumann et al., 2005; Lunney et al., 2016). Thus, methods other than vaccination must be explored to aid in fighting this pandemic; genetic improvement of the host is one of these methods (Lewis et al., 2007).

Over the past decades, genetic selection has been very effective at developing and improving lines of pigs that produce high-quality lean pork in an efficient manner (Dekkers et al., 2010). This has been accomplished by systematic selection on estimates of the breeding value of potential parent stock based on extensive phenotype recording for growth rate, backfat, meat quality, and reproduction. In principle, these same selection methods can be applied to identify and select pigs that are more resistant, tolerant, or resilient to diseases, provided these is at least partially determined by the genetics of the pig (i.e. the traits are heritable) and phenotypes related to disease resistance, tolerance, or resilience can be collected on breeding stock. Here, resistance refers to the ability of an animal to prevent infection when exposed to a pathogen or to limit replication of the pathogen when infected (Bishop, 2012). Tolerance refers to ability of an animal to maintain performance at a given level of infection or pathogen load (Bishop, 2012). Thus, at a given level of viremia, growth and performance of tolerant animals is less affected than that of less tolerant animals. Whereas tolerance refers to the impact on performance of a given pathogen load that is present in the animal, the concepts of resilience and robustness refer to the ability of an animal to maintain performance upon exposure to a pathogen. Thus, resilience combines resistance and tolerance (Doeschl-Wilson et al., 2012).

Early work that investigated a host genetic component to host response to PRRS revealed more gross lung lesions in PRRSV infected Hampshire pigs compared to Duroc and Meishan pigs (Halbur et al., 1998). With a sow model, Lowe et al. (2005) found that genetics may affect the rate of PRRSV-induced abortions, possibly due to levels of circulating IFNγ-secreting cells. Vincent et al. (2005, 2006) found that macrophage responses were partially predictive of breed and line associations with PRRSV resistance. Petry et al. (2005) found that a Large White/Landrace synthetic line had lower rectal temperatures and less viremia when infected with PRRSV compared to a Hampshire/Duroc synthetic line. Petry et al. (2007) found that, pre-infection, pigs that were less susceptible to PRRSV had higher levels of serum IL-8. Estimates of heritability of PRRSV resistance or resilience have been scarce but estimates for numbers born alive, stillborn, and mummies from sows infected with PRRSV range from 0.12 to 0.15 (Lewis et al., 2009). Rashidi et al. (2014) showed how reproductive performance data collected on commercial farms could be used to identify outbreaks of disease, specifically PRRS, which was used by Mathur et al. (2014) to obtain a quantitative measure of challenge load. Herrero-Medrano et al. (2015) showed how these data could be used to estimate genetic parameters for reproductive performance under different levels of challenge, which can be incorporated in breeding programs to select for disease resilience.

Although this research demonstrated that host response to PRRS has an important genetic component, collection of phenotypic data on the effects of PRRSV infection in breeding stock is problematic because of the need to maintain a high health status in nucleus breeding and multiplier herds. However, if genes or genetic markers linked to genes that are associated with resistance or susceptibility of pigs to the PRRSV infection can be identified, this can provide opportunities to select pigs using marker-assisted selection or genomic selection. Opportunities to investigate the role of host genetics on disease resistance have expanded greatly in the past decade through the rapid developments that have taken place in genomics and in genomics technology. These developments now allow animals to be genotyped for thousands of genetic markers (single nucleotide polymorphisms or SNPs) across the genome, allowing SNPs that are associated with traits of interest to be identified by genome-wide association studies (Goddard and Hayes, 2009).

The purpose of this review is to describe ongoing efforts to investigate opportunities to use the genetics of the pig as another tool in the fight against PRRS, as part of the PRRS Host Genetics Consortium (PHGC). The PHGC was established in 2007 with funding from the National Pork Board to investigate the genetic basis of host response to PRRSV infection, following extensive stakeholder input (NC229 PRRS disease researchers, NC1037/NRSP8 genome researchers, National Pork Board Swine Health and Animal Science Committee members, veterinarians, the American Association of Swine Veterinarians, producers, and commercial partners representing breeders, animal health, feed, and diagnostic companies) (Lunney et al., 2011; Rowland et al., 2012). Using novel genotyping and deep phenotyping approaches that combine state of the art genomics with state of the art virology, the ultimate goal of these efforts is to develop tools and selection criteria that can be used in pig breeding programs to lessen the impact of PRRS on the pork industry. Although substantial work is also underway on the genetic basis of reproductive PRRS (summarized in Dekkers et al., 2014 and Harding et al., 2016), the main focus of this review is on completed and ongoing research on PRRS during the growing phase as part of the PHGC. The main results of these studies are summarized in Table 1 and will be described in more detail in the remainder of this review.

The focus of this review is on opportunities to capitalize on genetic variation that is already present in swine populations through genetic selection, rather than on opportunities to generate new variation through methods such as gene editing. The latter has, however, recently demonstrated to provide opportunities to generate pigs that demonstrate complete resistance to PRRSV infection (Whitworth et al., 2016). The use of these methods for commercial pork production is, however, contingent on approval by relevant government agencies, which is at the moment uncertain.

2. PRRS host genomics consortium PRRSV infection trials

The experimental design for the PHGC trials consists of collecting comprehensive phenotypic, immunological, and genomic data on large numbers of commercial pigs under a nursery pig challenge model. In this model, groups of 200 weaned piglets from a commercial genetic source are challenged with a specific strain of the PRRSV at biosecure facilities at Kansas State University, and followed for 42 days post-infection (dpi) (for details see Lunney et al., 2011 and Boddicker et al., 2012). The purpose of the PHGC trials is not to compare different genetic products but to evaluate differences in host response between pigs from the same genetic cross. In fact, because of the complete confounding between trial and genetic line, the PHGC design does not allow comparisons between genetic sources to be made.

In the PHGC trials, all pigs are infected and all are genotyped for > 60,000 single-nucleotide polymorphisms (SNPs) using the Porcine SNP60 BeadChip (Ramos et al., 2009). Data are stored and available to PHGC members through a secure relational database (http://www.animalgenome.org/lunney/index.php), with access managed by a Cooperative Research and Development Agreement Material Transfer Agreement that is maintained by USDA ARS. All research results are public under that Agreement and, upon request, data and samples collected through the PHGC can be used by qualified researchers for further investigations.

In the first generation of PHGC trials, 9 groups of commercial crossbred nursery pigs from 6 genetic sources were experimentally infected with the NVSL 97 strain of the virus (Truong et al., 2004). A second generation of 5 PHGC trials involved experimental infection of similar lines of pigs with the more recent KS-2006-72109 PRRSV strain, which is 89% identical to the NVSL 97 strain at the viral GP5 peptide sequence level (Ladinig et al., 2015).

Table 1
Summary of main results of investigations into the genetic basis of host response to Porcine Reproductive and Respiratory Syndrome virus infection in nursery pigs.

	Experiment	# trials	# pigs	Main results	References
Generation 1 PHGC trials	Experimental infection with NVSL 97	9	1499	Host response to PRRS is moderately heritable Identification of a major gene for resistance and resilience on SSC4	Boddicker et al. (2012, 2013, 2014)
Generation 2 PHGC trials	Experimental infection with KS-2006-72109	5	845	Confirmation of the SSC4 effect for a second strain	Hess et al. (2016)
Generation 1 and 2 PHGC trials		14	2344	High genetic correlations between host response to heterologous strains Host response to PRRS is highly polygenic, beyond the SSC4 effect Genomic prediction of host response within and across strains	Waide et al. (2017) Waide (2015)
Generation 3 PHGC trials	PRRS vaccination and experimental co-infection with PCV2b	4	660	Confirmation of the SSC4 effect on vaccine and co-infection response Negative impact of PRRS vaccination on PCV2b response	Dunkelberger et al. (2017)
Field trials	Clean pigs in natural challenge barns	4	~800	In progress	
Antibody response	PRRSV specific IgG from PRRS infection trials	4	1189	MHC identified as major gene for IgG	Hess et al. (2016)
Gene expression experiments	Micro-array and RNAseq of selected pigs from the PRRS infection trials			Identification of GBP5 as the causal mutation for the SSC4 major gene Identification of genes and pathways associated with high and low viremia and the SSC4 major gene	Koltes et al. (2015) Arceo et al. (2013); Schroyen et al. (2015); Bao et al. (2016)

3. Phenotypic and genetic parameters for host response to experimental PRRSV infection

Host response to infection is characterized by weight gain (WG) from 0 to 42 dpi, a measure of resilience, and by viral load (VL), quantified as area under the curve of log-transformed (base 10) viremia in blood based on quantitative PCR from 0 to 21 dpi (Boddicker et al., 2012), which is a measure of resistance. Viremia after 21 dpi was characterized by 17 and 6% of pigs showing viremia rebound for NVSL and KS06 infections, respectively (Hess et al., 2016), characterized by statistical evidence of an increase in the level of serum viremia, following Islam et al. (2013). This likely reflects escape of the PRRSV from the host's immune response. Genetics of the host was found to have little impact on whether or not a particular pig showed rebound, as the heritability of rebound was close to zero ($0.03 \pm \underline{0.08}$) (Boddicker et al., 2012). The NVSL strain was found to be more virulent than KS06 because it reached higher peak viremia more rapidly and resulted in a 16% higher VL and 19% slower growth of the pigs (Hess et al., 2016). However, KS06 resulted in a more persistent infection over time. The phenotypic correlation between VL and WG was small negative: -0.33 for NVSL and -0.23 for KS06 (Hess et al., 2016).

Nevertheless, estimates of heritability were moderately high for both PRRSV isolates for VL (0.31 ± 0.06 for NVSL and 0.51 ± 0.09 for KS06) and for WG (NVSL: 0.33 ± 0.06 for NVSL and 0.31 ± 0.09 for KS06), indicating that 30–50% of the variation in host response of nursery pigs from the same cross following experimental PRRSV infection is due to differences in host genetics (Hess et al., 2016). Genetic correlations between VL and WG were substantial and negative for both NVSL (-0.74 ± 0.10) and KS06 (-0.52 ± 0.17), suggesting that genes that make pigs more resistant (lower VL) also tend to allow pigs to grow faster following PRRSV infection (Hess et al., 2016).

Some genetic crosses were used in infection trials with both PRRSV strains, which allowed the genetic similarity of host response to two different PRRSV strains to be assessed. Using these data, the genetic correlation of VL following NVLS infection with VL following infection with KS06 was estimated at 0.86 (± 0.19) and a similar estimate was obtained for WG (0.86 ± 0.27) (Hess et al., 2016). Together, these results demonstrated that host response to experimental infection with the PRRSV has a sizeable genetic component and that the genetic control of this response is very similar between PRRSV strains.

4. Discovery of a major gene for host response to PRRSV

To identify genetic markers and regions of the genome that are associated with viral load or growth rate following PRRSV infection, all pigs were genotyped with the 60k SNP panel and evaluated in genome-wide association studies (GWAS). Analyses of the NVSL trials identified a region on swine chromosome 4 (SSC4) of about ½ Mb in length that was associated with both VL and WG (Boddicker et al., 2012, 2013, 2014). This SSC4 region explained approximately 15% of the genetic variance for VL and 11% of the genetic variance for WG, indicating the presence of a major gene for host response to PRRS in that region. The ½ Mb region was found to be in high linkage disequilibrium across all breeds and lines investigated, which means that it is a region with very little recombination. One SNP in the region, WUR10000125, was found to capture the full effects of the region on VL and WG and this SNP (abbreviated WUR) was used in subsequent analyses. The WUR SNP was found to have significant effects in all trials, with individuals with genotype AB having 5% lower VL and 14% higher WG than pigs with the AA genotype at this SNP. Although the frequency of BB pigs was low, the BB genotype had similar effects as the AB genotype, suggesting the B allele to be dominant over the A allele. The B allele was found to be present in all breeds and lines that contributed to the PHGC trials but at a low frequency (2–40%) (Boddicker et al., 2014).

The WUR SNP also had a significant effect on VL following infection with the KS06 strain, indicating that the effects of this region may be

present across multiple strains of the PRRSV. Estimates of the effect were, however, smaller than observed for the NVSL 97 strain, about 82% of the effect for VL and about 19% of the effect on WG; the effect on WG was not significant (Hess et al., 2016). The smaller effects of this major gene for the KS06 strain, in particular for WG, may reflect the lower pathogenicity of the KS06 strain, consistent with the lower VL and higher WG observed for that strain compared to the NVSL strain.

Abella et al. (2016) recently showed that genotype at WUR was also associated with growth rate following vaccination with an attenuated European strain of the PRRSV. However, when pigs were challenged with a wild-type European PRRSV strain, genotype at WUR was not significantly associated with VL, although pigs with the AB genotype had numerically lower VL (Abella et al., 2016). Both these studies were, however, based on small numbers (n = 40 and 80).

Overall, these results show that the SSC4 region may confer some level of resistance and resilience to infection across PRRSV strains and could be used to select pigs for increased resistance and resilience by selecting for the B allele at the WUR SNP or by producing commercial crossbred pigs that have the AB genotype. Abella et al. (2016), however, also found pigs with the AB genotype at the WUR SNP to have lower growth rate during the grow-finish period in the absence of PRRS, which raises concerns about selecting pigs based on AB genotype at the WUR SNP. In work in progress, we have, however, not been able to replicate this finding in other commercial lines grown in clean environments and kept until market weight (Dunkelberger et al., 2017).

The ½ Mb SSC4 region includes multiple candidate genes that are known to be associated with innate immune response, including members of the guanylate binding protein (GBP) family (GBP1, GBP2, GBP4, GBP5, and GBP6), CCBL2, GTF2B, and PKN2 (Boddicker et al., 2012). Because of the high linkage disequilibrium in the SSC4 region, fine mapping the causative mutation for the SSC4 effect by genetic mapping approaches was problematic. Instead, a functional genomics approach was used, involving the evaluation and analysis of the expression of genes in the region. For this purpose, blood samples at 5 time points from 8 pairs of littermates from one of the PHGC trials, with one piglet being AA and one piglet being AB for the WUR SNP, were subjected to RNA-sequencing analyses. Results identified one candidate gene in the SSC4 region that showed significantly higher expression in AB versus AA piglets across multiple time points during the trial (Koltes et al., 2015). In addition, allele-specific expression was identified for this gene in AB piglets, with the B allele being expressed more frequently than the A allele across multiple time points. Subsequent analyses of the sequence data identified a splice site variant in one of the introns of this gene, which results in a premature stop codon in transcripts produced by the A allele, and thus in production of an incomplete protein (Koltes et al., 2015). Considering the full genome-wide RNA-sequencing data from this experiment, Schroyen et al. (2016) identified additional differences in expression patterns of genes across the genome over time between AA and AB animals, in particular for several modules of genes that were identified using weighted gene co-expression network analyses. Minor differences between AA and AB animals were observed in genes associated with immune response and DNA damage response but a highly significant difference in expression was identified in genes associated with ion transport/homeostasis and the participation of G-coupled protein receptors, which was reinforced by results from regulatory and phenotypic impact factor analyses between the AA and BB genotypes. Based on these results, Schroyen et al. (2016) hypothesized that these gene expression differences are the result of a reduced ability of the truncated GBP5 of the AA genotype pigs to inhibit viral entry and replication as quickly as the intact GBP5 protein of the AB genotyped pigs.

Guanylate binding proteins (GBPs) are well known to have interferon-inducible activity against intra cellular bacteria and parasites (Kim et al., 2012). A recent study by Krapp et al. (2016) concluded that GBP5 impairs infectivity of the HIV virus by demonstrating that GBP5 levels in macrophages determine and inversely correlate with infectious HIV-1 yield. They also showed that mutant GBP5 proteins that are truncated in a similar region as the transcripts produced by the WUR A allele in our studies, lose their anti-HIV activity, thus potentially accounting for the higher PRRSV levels found in AA pigs. Although we don't have functional proof of the impact of the GBP5 splice site variant on PRRSV, these results for HIV are promising. Another study in pigs, however, found that a polymorphism in exon 2 of GBP1, which is also located in the SSC4 region, was associated with viremia levels and weight gain in pigs infected with PRRSV (Niu et al., 2016). In that study of 38 PRRSV infected pigs, the WUR SNP did not show a significant association with viremia or weight gain.

5. Selection for host response to PRRS by whole-genome prediction

Although the major gene described in the previous section can be used to select pigs that are more resistant or resilient to PRRS, it only explains a portion (10–15%) of the genetic differences in host response to PRRSV infection. A complete GWAS of host response using the PHGC trial data revealed no other genomic regions with substantial effects (Waide et al., 2017). Instead, beyond the SSC4 region, the genetic basis of host response was found to be highly polygenic, meaning that genetic differences in host response are determined by many genes across the genome, each with a relatively small effect but adding up to a substantial heritable effect. In addition, apart from the SSC4 region, there was little to no overlap of significant regions for host response to the NVSL versus the KS06 virus. However, genes near associated SNPs were enriched for the same gene ontology terms across PRRSV isolates, suggesting host responses to these two isolates are affected by similar biological processes (Waide et al., 2017), which is consistent with the high genetic correlation of host response to these two isolates (Hess et al., 2016).

These results suggest that it may not be possible to identify a limited number of markers that together explain a large proportion of the genetic differences in host response to PRRS for use in marker-assisted selection. This is a common finding in quantitative genetics and has been referred to as the missing heritability problem in human genetics (Manolio et al., 2009). A solution to this problem is to use whole-genome or genomic prediction, which uses tens of thousands of markers across the genome to predict an individual's breeding value for a trait, rather than just markers that have been found to be significant in a GWAS. Genomic prediction and selection involve estimation of the effects of all markers on the genotyping panel (> 40,000 in our case after quality control), using a training population that consists of animals that have been genotyped and phenotyped, and then applying the resulting SNP effect estimates to predict the genetic value of other animals that have been genotyped but have no phenotype (Meuwissen et al., 2001). Genomic prediction has been successfully implemented in dairy cattle, allowing selection of bulls at a young age, prior to them having completed their progeny test, based only on their SNP genotypes across the genome (Hayes et al., 2009). This has resulted in a nearly doubling of the rate of genetic progress in dairy cattle through a reduction of the generation interval (Schaeffer, 2006; Schefers and Weigel, 2012). Genomic prediction has also been implemented in other livestock species, including pigs (Van Eenennaam et al., 2014). Although opportunities to reduce generation intervals are limited in pigs, because boars and gilts to produce the next generation are typically selected prior to sexual maturity, genomic prediction does allow for an increase in the accuracy of estimated breeding values at the point of selection. This is particularly beneficial for reproduction and meat quality traits, for which phenotypic records are not available on selection candidates at the point of selection (Van Eenennaam et al., 2014).

Genomic prediction also offers solutions for selection for traits that cannot be measured on animals that are being selected in a breeding program because they must be kept in facilities with high biosecurity

(nucleus and multiplier herds), which includes health or disease resistance. Thus, the host response data that has been collected in the PHGC trials could be used as a training population for genomic prediction of host response of animals in pig nucleus breeding programs. To evaluate the potential of such a genomic prediction and selection strategy, we used the PHGC trial data in a cross-validation analysis of genomic prediction. This involved splitting the PHGC data in training and validation data sets, allowing genomic predictions to be developed based on the training data and applied to the validation data. The accuracy of the genomic predictions was then evaluated based on the correlation between the predictions and host-response phenotypes in the validation data. To convert this correlation to the accuracy of predicting the genetic value for host response, the correlation was divided by the square root of heritability of the trait. Because the PRRSV strains that pigs encounter in the field will be different from the strains used in the PHGC trials, we focused on across-strain genomic prediction of host response by training on PHGC trials that used one strain (NVSL or KS06) and validated on PHGC trials that used the other strain. The resulting accuracy of genomic prediction of VL was 0.45 when training on the KS06 data and validating on the NVLS data and 0.34 when training on the NVSL data and validating on the KS06 data (Waide, 2015). For comparison, the accuracy of predicting an animal's genetic value for a trait based on the animal's own phenotype is the square root of heritability (Falconer and MacKay, 1996), which amounts to 0.56 for NVSL and 0.71 for KS06. Thus, genomic predictions were over half as accurate as recording host response directly on the selection candidates. The latter would, however, require pigs in nucleus herds to be challenged with PRRSV, which is of course not feasible in a breeding program. Thus, these results show that genomic prediction can be a useful tool to select for improved host response to PRRSV infection across strains. However, substantial data sets with phenotypes and genotypes on challenged individuals are needed. In addition, a large proportion of this predictive ability came from the GBP5 region; when the GBP5 region was excluded from the prediction model, accuracies dropped to 0.12 for both training/validation data sets, reflecting the highly polygenic basis of the effects of the rest of the genome on host response.

6. Antibody response

Antibody response to PRRSV infection was evaluated in several PHGC trials using Fluorescent Microsphere Immunoassay, evaluated as the sample to positive ratio (S:P) of PRRSV N-protein specific IgG in serum at 42 dpi (Hess et al., 2016). The S:P ratio was found to be moderately heritable for both strains (0.31 ± 0.09 for NVSL and 0.40 ± 0.10 for KS06) but did not have a clear relationship with VL or WG following infection, either at the phenotypic or genetic level (Hess et al., 2016). However, GWAS identified strong associations of SNPs in the Major Histocompatibility Complex with antibody response, which explained ~10 and 45% of the genetic variance of S:P ratio for NVSL and KS06, respectively. The WUR SNP was not associated with antibody response, confirming that the mode of action of the major gene in this region is likely not through adaptive antibody-mediated immune responses.

Together, these findings suggest that antibody response to PRRSV infection could be a possible indicator trait for selection of pigs with increased resistance to PRRSV infection. This proposition is further strengthened by results from an outbreak in a reproductive sow herd reported by Serão et al. (2014), which found high favorable genetic correlations of S:P ratio measured by ELISA ~46 days after the outbreak with reproductive performance (litter size, number stillborn, number mummies) during the outbreak. Indeed, further studies indicated moderate genomic prediction accuracies for PRRS S:P ratio using SNPs located within two genomic regions on SSC7 that had large effects on S:P ratio, while the rest of the genome showed limited predictive ability (Serão et al., 2016). Further work is needed to confirm these associations, as well as the relationship of S:P ratio following vaccination with host response and performance during PRRS infection. The latter would be needed in order to implement S:P ratio as an indicator trait in selection programs.

7. Additional gene expression and immune response analyses

To further investigate the dynamics of host response to PRRRV infection and immunological and genetic pathways that are involved in this response, several gene and protein expression analyses have been completed or are underway. Initial work using microarrays showed a number of genes that were differentially expressed between animals with high and low host response to PRRS (Arceo et al., 2013). Using microarray gene expression profiles, Schroyen et al. (2015) identified differences in blood RNA patterns in early responses to PRRSV infection between pigs with extreme phenotypes or with a different WUR genotype. Differences were, however, subtle but could be revealed through gene network and co-expression analyses. The expression pattern of one such cluster of genes was associated with WG and with WUR genotype and contained numerous immune response genes such as cytokines, chemokines, interferon type I stimulated genes, apoptotic genes and genes regulating complement activation (Schroyen et al. (2015)).

More detailed RNA-sequencing analyses of globin-depleted blood RNA focused on gene expression changes over time and between pigs that show different anti-viral responses (Choi et al., 2014; Bao et al., 2016). Inter-individual differences in gene expression were evaluated at each day and resulted in evidence of *cis*-acting expression quantitative trait loci (*cis*-eQTL) for approximately 900 genes. Associations between *cis*-eQTL markers and phenotypes using 383 pigs indicated host genotype-dependent reduced expression of several genes, including GBP5, as expected from our earlier mapping results. These alleles contribute to higher viremia levels or lower weight gain in response to PRRSV infection. These studies have expanded our understanding of disease control mechanisms and provide potential new biomarkers that can be measured in blood as indicator traits for disease. Further studies are needed to define the causal mutations that regulate expression of these candidate susceptibility genes.

Serum cytokine and chemokines evaluations have further highlighted the importance of early interferon-α levels. All PRRSV infected pigs had high 4 dpi serum interferon-α levels; however, pigs with higher viral loads continued to express interferon-α, whereas those with lower viral loads quickly return to pre-infection levels (Choi et al., 2013).

8. Co-infection trials

In practice, PRRS is often found to increase incidence of secondary infections, resulting in e.g. porcine respiratory disease complex (PRDC) and porcine circovirus associated disease (PCVAD) (Baekbo et al., 2012). To investigate the genetic basis of host response to co-infection, four co-infection trials were conducted at Kansas State University, in which nursery pigs were infected with field strains of PRRSV and PCV2b. To evaluate host response to PRRS vaccination, half of the pigs in each trial were vaccinated with a modified live PRRSV 28 days prior to co-infection. Details of the design of these experiments, along with results for pathogenesis and the effects of PRRSV vaccination are in Niederwerder et al. (2015). Results showed that vaccination to PRRS increased the impact of subsequent exposure to PCV2b, consistent with earlier findings that PRRSV infection weakens the immune system and increases the susceptible of pigs to other pathogens (Yin et al., 2013). Genetic analyses of the first two trials by Dunkelberger et al. (2017) demonstrated a low to moderate genetic basis for host response to PRRS vaccination (PRRS VL and WG) and to co-infection (PRRS and PCV2b VL and WG with or without prior vaccination), with heritabilities ranging from 0.07 to 0.57. Genotype at the WUR SNP had a significant

association with host response, both post vaccination and post co-infection: post-vaccination, AB pigs had lower vaccine virus VL and faster gain than AA pigs, confirming results by Abella et al. (2016) for vaccination with an attenuated European strain of the PRRSV. Post co-infection, AB pigs had lower PRRSV VL but did not significantly differ from AA pigs in growth rate. For PCV2b VL, suggestive evidence of an interaction between vaccination and WUR genotype was detected, where AB pigs had significantly lower PCV2b VL when vaccinated but similar PCV2b VL when they were not vaccinated. This demonstrates that the major gene for PRRS resistance on SSC4 not only provides some level of resistance against PRRS infection but also reduces the level of co-infection with or following PRRSV infection.

9. Field studies

While experimental infection trials provide great opportunities to investigate the genetic basis of host response under controlled conditions, these finding must be validated in the field. Field studies also allow additional effects to be observed and investigated. Multiple field studies are underway to evaluate host response to disease in growing pigs in the field. These studies involve introducing 200 clean nursery pigs with known WUR genotype into 'health-challenged' finishing barns. Pigs are repeatedly weighed and bled and followed all the way to market.

10. Conclusions

Host response of nursery pigs to PRRSV infection was found to have a sizeable genetic component under controlled experimental challenge studies. In particular, a major gene for host response to PRRS was identified on SSC4. A putative causative mutation was identified in the GBP5 gene, which is involved in innate immune response. Pigs with the favorable genotype for this gene have been shown to have improved host response to two different Type I strains of PRRSV, as well as to vaccine strains of both Type I and Type II modified live viruses. The WUR SNP in this region can be used to select for pigs that are more resistant and resilient to PRRS. While this comprehensive suite of studies is unlikely to identify pigs that are completely resistant to PRRS, they are starting to unravel the genetic basis of host response to PRRS, leading to the ability to select pigs that are less susceptible to PRRSV infection and to the effects of PRRS on performance. This work demonstrates that, although genetic selection will not offer a single 'magic bullet' solution, i.e. complete resistance, especially given the complexity and variability of the PRRS virus, host genetics can be an additional and complementary approach to fight the impact of PRRS on pork production. In addition, insight into host response to PRRSV infection can lead to new avenues for development of more effective vaccines and therapeutics.

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